Development of postural control in infancy in cerebral palsy and cystic periventricular leukomalacia

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Abstract

Background: Development of postural problems in Cerebral Palsy (CP) is largely unknown. Postural muscle activity is organized into two levels: 1) direction-specificity; 2) fine-tuning of direction-specific activity.

Aim: To study development of postural control until 21 months corrected age in subgroups of infants at very high-risk (VHR) of CP: a) with and without CP at 21 months; b) with and without cystic periventricular leukomalacia (cPVL), the brain lesion with highest risk of CP.

Methods and procedures: Longitudinal electromyography recordings of postural muscles during reaching were made in 38 VHR-infants (severe brain lesion or clear neurological signs) between 4.7 and 22.6 months (18 CP, of which 8 with cPVL). Developmental trajectories were calculated using linear mixed effect models.

Outcomes and results: VHR-infants with and without CP showed virtually similar postural development throughout infancy. The subgroup of VHR-infants with cPVL improved performance in direction-specificity with increasing age, while they performed throughout infancy worse in fine-tuning of postural adjustments than infants without cPVL.

Conclusions and implications: VHR-infants with and without CP have a similar postural development that differs from published trajectories of typically developing infants. Infants with cPVL present from early age onwards dysfunctions in fine-tuning of postural adjustments; they focus on direction-specificity.

What this paper adds?

Cerebral palsy (CP) is a heterogeneous group of disorders characterized by motor impairments and postural dysfunctions resulting from injury to the developing brain. Previous research indicated that infants at high risk of CP do not show postural deficits at early age, but 'grow into a postural deficit'. We evaluated postural control until 21 months corrected age of infants at very high risk of CP (VHR-infants), mostly due to a brain lesion. Cystic periventricular leukomalacia (cPVL) is a marked brain lesion carrying highest risk of CP. Our study had two main findings: 1) not only VHR-infants who develop CP grow into a postural deficit, but also VHR-infants who do not develop CP. The majority of the latter showed minor neurological dysfunction (MND) at 21 months. This suggests that postural impairments of infants with a neonatal brain lesion resulting in MND resemble those of CP; 2) Postural development of VHR-infants with cPVL, differs from that of VHR-infants with other brain lesions. They show dysfunctions in the fine-tuning of postural adjustments from early age onwards, while they continue to improve the basic level of direction-specificity throughout infancy. In contrast, VHR-infants without cPVL do not change the use of direction-specific adjustments throughout infancy, but improve fine-tuning of postural adjustments. Possibly, the diffuse white matter injury in cPVL results in serious impairment of the second level, shifting focus of postural control to the first level. The results suggest that infants with cPVL may need an early intervention approach that differs from that of other VHR-infants.

Introduction

Cerebral palsy (CP) is a heterogeneous group of disorders in which motor impairment and postural dysfunction are of primary concern.[1] Postural control plays a pivotal role in mobility, and has two major functions: 1) to provide a reference posture in which the projection of the centre of gravity of an individual stays within the supporting surface to maintain balance; 2) to provide a reference frame to the environment. The position and orientation of body parts influence the coordination of an upcoming action.[2] Impaired postural control in children with CP may thus, for example, lead to a delay or absence of the development of milestones such as reaching, sitting or walking, implying that the postural dysfunction results in activity limitations and limitations of functional performance in daily life.[1] Studying the underlying mechanisms of postural dysfunction in infants at high risk of CP is important to develop appropriate early intervention strategies.

In terms of muscle coordination two levels of postural control are distinguished.[3] The basic level is direction-specificity: during forward body-sway, activity of the dorsal muscles precedes that of the ventral muscles. Previous research showed that when typically developing (TD) infants learned to reach around the age of 4 months about 40–50% of the reaching movements was accompanied by direction-specific adjustments. Other studies suggested that the prevalence of direction-specific adjustments increases with age to 60–80% at 18 months[4] and 100% at 2 years.[5] Most children with CP are able to generate directionally appropriate adjustments[6], but in infants at high risk of CP the increase of direction-specific adjustments during infancy develops at a slower pace.[7] The limited data available – only two children were evaluated – suggested that direction-specificity is absent in children with CP functioning at Gross Motor Function Classification System (GMFCS)[8] level V.[9,10]

At the second level of postural control, the direction-specific adjustments are adapted to the task demands.[3] Adaptations may consist of changes in the selection of specific direction-specific muscles, the latencies to muscle activation, recruitment order and anticipatory muscle activity. The most subtle form of adaptation is modulation of postural EMG-amplitude to e.g. specifics of the sitting position or the kinematic characteristics of the reaching movement.[3] At school age virtually all children with CP present dysfunctions at the second level of control. During reaching movements they have a stereotyped preference for the top-down recruitment order in which the dorsal neck muscle is activated prior to dorsal trunk muscles[6], and have a reduced capability to adapt the degree of muscle contraction to the specifics of the sitting position.[11] A similar picture emerges from the studies

on postural control in children with CP that use Centre of Pressure measurements. Infants who later were diagnosed with CP exhibited less postural strategies and had a limited ability to select postural strategies compared to TD-infants.[12]

General conclusions on postural control in CP are difficult, due to its heterogeneity in causes and clinical expression. Knowledge on differences in postural control between infants at very high risk of CP (VHR-infants) developing CP, and VHR-infants without CP – but who usually develop clinically relevant forms of minor neurological dysfunction[13] – is lacking. Also, the pathophysiology of the development of postural problems in CP has not been addressed yet. For example, the effect of different types of brain lesions on atypical development of postural muscle coordination in children with CP has not been studied.

The systematic review of Hielkema and Hadders-Algra showed that 86% of infants with the brain lesion cystic periventricular leukomalacia (cPVL) developed CP (median value).[14] These infants have a poor motor function and function at the highest, i.e., worst, GMFCS levels.[15] The same review indicated that infants with preterm parenchymal lesions and periventricular haemorrhagic infarction developed CP in 71% of the cases and infants with term stroke, usually with a focal or cortical localization without damage to the periventricular zone, developed CP in 29% of the cases.[14] In addition, Jacobs et al. reported that term infants with moderate to severe encephalopathy and signs of hypoxia-ischemia after asphyxia were diagnosed with CP in 27–29% of the cases.[16] Limited evidence suggests that preschool and school aged children with injury of the periventricular white matter have impaired postural adjustments: Mewasingh et al. assessed postural strategies by Gestalt observation;[17] Hadders-Algra et al. studied postural adjustments with surface EMGs.[9] However, most of the children in the latter study had milder forms of periventricular leukomalacia and did not develop CP.

The aim of the present study is to assess the development of muscular postural strategies in subgroups of VHR-infants. We hypothesize that VHR-infants developing CP, in contrast to VHR-infants not diagnosed with CP, grow into a postural deficit with increasing age.[7] It implies that the deficit becomes apparent later in infancy; this corresponds to the clinical picture that CP in general cannot reliably be diagnosed before 18 months.[18,19] We expect that the deficits in both levels of postural control in CP will become apparent after the first year of life and consist of a delayed development of postural activity at the first level and significant impairments at the second level.[6,7] Additionally, we hypothesize that infants with the brain lesion cPVL have problems in both levels of postural control from early age onwards, therewith differing from other VHR-infants (with other brain lesions).[20,21] We predict that in infants with cPVL direction-specificity is severely impaired and shows

a marked developmental delay; in addition we expect severe impairments at the second level of control. We addressed the following questions: i) Does the development of postural control of VHR-infants who are diagnosed with CP at 21 months corrected age (CA) differ from that of VHR-infants not diagnosed with CP? ii) Does the development of postural control of the subgroup of VHR-infants with the most severe neonatal brain lesion cPVL differ from that of all other infants at very high risk of CP?

Material and methods

Participants

Forty-three VHR-infants were enrolled in the LEARN2MOVE 0–2 study (L2M 0–2) before 9 months CA. L2M 0–2 evaluates the effects of two types of early intervention applied during 12 months. Inclusion criteria were: a) cystic periventricular leukomalacia; b) parenchymal brain lesion; c) severe asphyxia followed by a lesion to the brain (identified on MRI); d) neurological abnormalities suggestive for the development of CP. Infants were excluded in case of a congenital disorder or if parents did not have a sufficient understanding of the Dutch language. L2M 0–2 was registered under trial number NTR1428. The medical ethical committee of the University Medical Center Groningen gave permission and the parents informed consent.[22]

MRI or cranial ultrasound data from the neonatal period (as part of usual clinical care) was available. An experienced paediatric neurologist blinded to clinical data classified the imaging data of the 40 infants who did not drop out of the study (MRI n=33, cranial ultrasound n=7) into i) basal ganglia/thalamic lesions, ii) cortical infarction (full-term border-zone infarction or middle cerebral artery infarction), iii) (cystic) periventricular leukomalacia, iv) posthemorrhagic porencephaly, v) non-specific lesions (e.g., ventriculomegaly) or no significant lesions.[21] As it is recommended not to diagnose CP too early in infancy,[18] and as some infants completed the intervention trial at 21 months CA, we diagnosed CP at this age on the basis of the Touwen Infant Neurological Examination.[23] CP implies the presence of a clear neurological syndrome, for example consisting of pathological reflexes, muscle tone dysregulation and abnormalities in posture and motility. When CP was diagnosed, severity was classified using the GMFCS.[8] In children without CP at 21

months CA the Hempel assessment was used;[24] children were classified as having the complex form of minor neurological dysfunction (MND), which is the clinically relevant form of MND, or as neurologically normal – including infants with simple MND, i.e., a normal, but non-optimal neurological condition.[13] The TINE and Hempel assessment show a good validity and reliability.[23,24]

Postural control and kinematic assessment

We aimed to assess postural control four times, i.e., at the start of the study (prior to 9 months CA), 6 and 12 months after enrolment and around 21 months CA. Infants were assessed in supine, supported and/or unsupported sitting condition. For the present study we focused on supported sitting position, as this provided the most complete longitudinal data set. Infants were seated in an infant chair providing trunk support, or – if uncooperative – on their parent's lap (n=7 sessions). Prior research showed that postural adjustments of infants sitting on their parent's lap resembled those of infants sitting in an infant chair.[4] Toys were presented to elicit reaching movements and their associated postural adjustments. We aimed for at least ten reaching movements with the right arm or – if the infant preferred the left arm – the left arm (right arm n=29, left n=7, changing during infancy n=2). If less than three reaching movements were present, data of this session were excluded from further analysis. If the infant became tired or started to cry, the session was stopped.

Continuous multiple surface electromyography (EMG) recordings were made of the following arm- and postural muscles on the preferred side of the body: Deltoid (DE), Biceps Brachii (BB), Triceps Brachii (TB), Pectoralis Major (PM), Neck Extensor (NE), Neck Flexor (NF), Rectus Abdominis (RA), Thoracal Extensor (TE), Lumbar Extensor (LE). Bipolar electrodes were attached with an interelectrode distance of 14 mm. The EMG-signals were continuously recorded by means of an electro-physiological front-end amplifier (Twente Medical Systems International, Enschede, the Netherlands), at a sampling rate of 500 Hz.

To assess modulation of EMG-amplitude with respect to kinematics, three reflective markers were placed on the preferred side of the body: the wrist, mandibular angle and lateral to the eye. A dual camera system with a sampling rate of 50 Hz registered continuous kinematic recordings.

Data analyses

PedEMG (Developmental Neurology, University Medical Center Groningen, The Netherlands[4]) was used for video and EMG-analysis. Reaching movements with the preferred arm, in a calm behavioural state and with few other movements were selected, and start and end of the reaching movement were indicated. The EMG-signal was synchronized with the video to identify reaching-related muscle activity. PedEMG uses the algorithm of Staude and Wolf to determine significant phasic bursts of EMG-activity.[25] Significant bursts of activation of the postural muscles were identified between 100 ms before activation of the first recruited arm muscle (prime mover) and the end (or first 1000 ms) of the reaching movement.[26]

EMG-parameters were calculated based on van Balen et al.[4] Firstly, activity on the first level of postural control was assessed: the direction-specificity at trunk and neck level. For example, direction-specific activity at trunk level indicates that (one of) the dorsal trunk muscle(s) are activated prior to (or in absence of activation of) the ventral muscle, i.e. the TE and/or LE are activated prior to or in absence of RA activation. Figure 1 displays an example of an EMG-recording showing direction-specific or no direction-specific activity in an infant with and an infant without cPVL. If the trial was direction-specific at trunk level, the following parameters of the second level of postural control were calculated: i) the complete pattern: the pattern of muscle activation in which all direction-specific postural muscles are recruited; ii) recruitment order, classified as top-down when the neck extensor is recruited prior to the thoracal and lumbar extensor and as bottom-up when the lumbar extensor is activated first. A simultaneous recruitment occurs if all postural muscles are activated within 20 ms; iii) anticipatory activation: activation of the postural muscle prior to the onset of the prime mover; iv) latencies: time difference between activation of the prime mover and the postural muscle.

The last parameter of the second level of postural control was mean EMG-amplitude. It was determined for three intervals after subtracting baseline activity: a) -100 ms to 0 ms (0 is the start of the prime mover), the interval reflects anticipatory postural muscle activity; b) 0–100 ms; c) 100–1000 ms. EMG-amplitudes cannot be evaluated longitudinally, as amplitudes are dependent on body proportions (subcutaneous fat, muscle length) and skin condition which may vary over days. We therefore assessed whether infants were able to modulate the degree of muscle contraction of the direction-specific muscles – using EMG-amplitudes – to specifics of the quality of the reaching movement and the degree of head sway within one session. To this end, kinematic data were retrieved from the video-recordings using SIMI Motion System Analysis (SIMI Reality Motion Systems GmbH, Unterschleissheim,

Germany). Parameters were: i) number of movement units (MU) of the wrist, where one MU consists of one acceleration and deceleration in the velocity profile of the reaching movement. The number of MUs reflects the degree of feedforward programming, with a movement of one MU indicating a perfectly preprogrammed movement;[27] ii) maximum velocity of the wrist marker; iii) average velocity of the wrist marker; iv) head sway, in which we calculated the total angular change of the vector between the markers at the mandibular angle and lateral to the eye. If the infant showed one or more statistically significant associations between an amplitude interval of a specific direction-specific muscle (NE, TE or LE) and a kinematic parameter, the child was classified as being able to modulate the amplitude of that muscle to reaching kinematics ('modulator'), and thus able to adapt to the reaching situation.

Statistical analyses

Current postural control data were collected as additional observational data from the L2M 0–2 project. Developmental outcome in both intervention groups was similar.[28] The studies of van Balen et al. (2012, 2015) using the same paradigm and methodology indicate that the method is sensitive and group sizes are sufficiently large to find effects.[4,7]

Descriptive statistics were carried out with SPSS, version 23. R version 3.3.1 was used to fit generalized linear mixed models with binomial link-function for all variables except latencies and amplitudes.[29] Linear predictor variables were age, group (CP versus no CP or cPVL versus non-cPVL) and an interaction term between age and group. The model takes repeated measurements into account by incorporating a random effect for intercept. The outcome describes the average developmental trajectory per group per outcome parameter. Developmental trajectories of the median latencies of the postural muscles were calculated using linear mixed effects models, using the natural logarithm of (0.15+median latency) to meet the model assumptions. All final mixed effects models were estimated using restricted maximum likelihood estimation, hence making optimal use of all data available and resulting in unbiased fixed effects estimates under the assumption of missing at random. The exp (β) represents the growth factor of the developmental trajectory. If the interaction term was significant, the age at which the difference became statistically significant was calculated ($p<0.05$). If the interaction term was not significant, only the model without interaction term is presented. Finally, to evaluate the infant's capacity to modulate EMG-amplitude, Spearman's rho was used to

explore correlations between the amplitude intervals and kinematic parameters per infant at the last assessment (21 months CA). Subsequently, if the child was classified as “modulator”, Fisher’s exact tests were used to test differences in the prevalences of ‘modulators’ between the infants with and without CP, and those with and without cPVL ($p<0.05$).

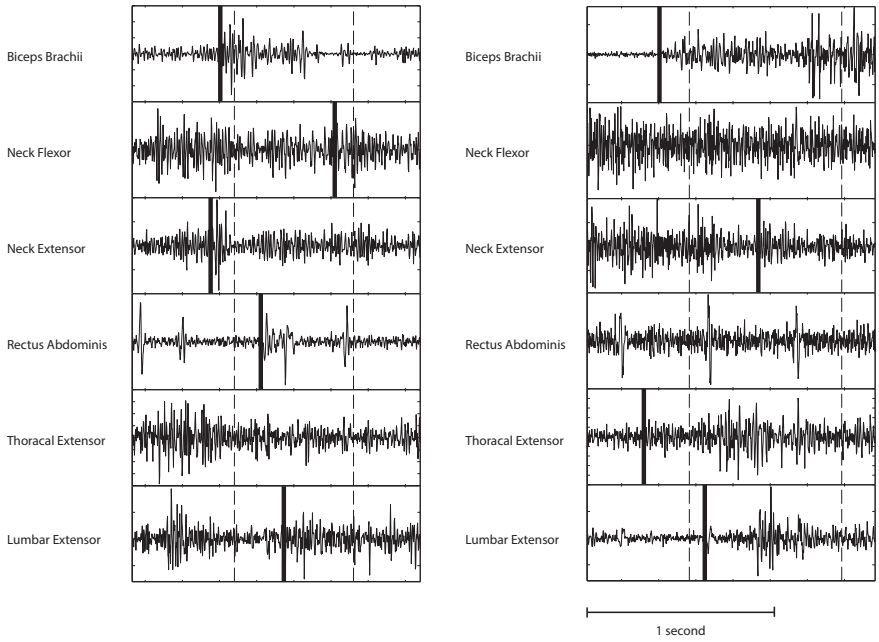

Figure 1: Examples of EMG-recordings of the prime mover and postural muscles. Vertical dotted lines indicate start and stop of the reaching movement. The bold vertical lines represent the start of muscle activation based on the algorithm of Staude and Wolf (1999). The small horizontal lines on the y-axis indicate the amplitude units with intervals of 50 μV. In the left panel a reaching movement of a 21-month-old VHR-infant without CP is shown. The neck extensor is active prior to the neck flexor, which indicates direction-specific activity at the neck level. The thoracal extensor is not active during the reaching movement – neither within the anticipatory window of 100 ms prior to activation of the prime mover – and activity in the rectus abdominis precedes that in the lumbar extensor: the reaching movement is not direction-specific at the trunk level. The right panel displays a reaching movement of a 21-month-old VHR-infant with cPVL and CP. The movement is direction-specific at the trunk level – the thoracal extensor is activated within 100 ms prior to activation of the prime mover -, but not at the neck level.

Results

From 38 of the 43 infants in L2M 0–2, at least one appropriate postural assessment in supported sitting position was available, resulting in a total of 103 assessments. Missing data of the other five infants occurred because infants were not able to sit in a chair (*n*=3) or dropped out of the study after one assessment in supine position (*n*=2). Missing sessions in the 38 included infants were due to: technical problems, only data in supine position available, infants did not tolerate EMG-electrodes and/or reflective markers or dropped out from the study after one or two sessions in sitting position. Table 1 displays baseline characteristics of the 38 infants.

Figure 2 displays the developmental trajectories of the different parameters for infants with and without CP and with and without cPVL.

First level of postural control

The mixed model analysis (Table 2) indicated that the percentage of direction-specific trials at the trunk level increased with age corrected for CP (OR 1.03, CI: 1.01–1.06), and that this development was similar in infants with and without CP. At the last assessment (21 months CA), the rate of direction-specificity was usually over 60%, see Figure 2. Infants with cPVL however, showed a modest increase in direction-specificity with increasing age (OR 1.11, CI: 1.04–1.17), whereas in infants without cPVL a similar increase was absent (OR 1.01, CI: 0.99–1.04). Infants with cPVL had significantly higher values than infants without cPVL at 21.0 months, but not before that age (21 months: median values 80% vs. 65%, respectively; Figure 2). The two children with GMFCS level V demonstrated at 21 months CA direction-specificity at the trunk level during 67% and 79% of the reaches (median values).

At the neck level, the rate of direction-specificity did not change with age in infants with CP (OR 1.00, CI: 0.96–1.04). However, in infants without CP direction-specificity in the neck decreased with increasing age (OR 0.92, CI: 0.89–0.95). Before the age of 11.4 months, infants without CP had more direction-specificity at the neck level compared to infants with CP, while after the age of 21.8 months, infants without CP had significantly lower levels than infants with CP. Note that 21.8 months is at the limit of our data, the result is based on the model, thus caution is needed for interpretation. Direction-specificity at the neck level decreased with increasing age after correction for cPVL (OR 0.95, CI: 0.93–0.98), but the development was similar in infants with and without cPVL (OR 1.25, CI: 0.84–1.86; Figure 2).

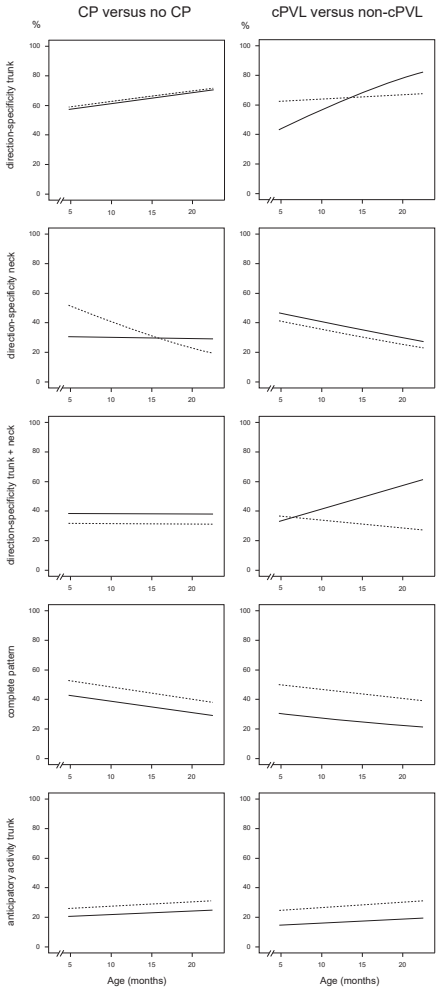

Figure 2: Developmental trajectories of EMG-parameters of infants with and without CP or cPVL. The graphs represent the average developmental trajectories of EMG-parameters throughout infancy. Parameters are displayed as percentages of the total amount of reaching movements. Continuous lines indicate the trajectories of VHR-infants diagnosed with CP or infants with cPVL, whereas the dotted lines display trajectories of VHR-infants without CP or without cPVL.

Table 1. Infant characteristics

Baseline characteristics	n=38
Sex, n (boys/girls)	25/13
Gestational age, weeks (median + range)	31.9 (25.9–41.4)
Birth weight, grams (median + range)	1794 (720–5400)
Age range of measurements, months	4.7–22.6
Type of brain lesion, n (diagnosis of CP at 21 months CA[a])	
Cortical infarction	3 (3)
Cystic periventricular leukomalacia	8 (8)
Periventricular leukomalacia[a]	3 (0)
Basal ganglia and/or thalamic lesion	6 (2)
Posthemorrhagic porencaphaly[b]	11 (5)
Non-specific or no significant lesions	7 (0)
Neurological outcome, n	
Normal	2
Complex form of minor neurological dysfunction	16
Cerebral Palsy	18
Unknown[b]	2
GMFCS level, n (infants with cPVL)	
I	3 (0)
II	7 (2)
III	4 (3)
IV	2 (1)
V	2 (2)

[a] Without cysts
[b] Of 2 infants with posthemorrhagic porencephaly no information on diagnosis of CP is available due to drop-out

Direction-specificity at both trunk and neck level did not change with increasing age when correcting for CP (OR 1.00, CI: 0.97–1.03), and the development was similar in infants with and without CP (OR 1.36, CI: 0.82–2.21). Median values at 21 months CA were usually over 28%. In infants with cPVL however, direction-specificity at both trunk and neck level increased with increasing age (OR 1.07, CI: 1.01–1.13), while it did not change throughout infancy in infants without cPVL (OR 0.98, CI: 0.95–1.00). From 13.0 months onwards, the infants with cPVL had a higher rate of direction-specificity at trunk and neck level than infants without cPVL. Median values were over 60% in cPVL and below 30% in non-cPVL at 21 months CA (Table 2; Figure 2).

Second level of postural control

The rate of developmental change (the interaction terms) for all secondary outcome parameters were similar for infants with and without CP and infants with and without cPVL. Therefore, only the models without interaction term are discussed and presented in Table 2.

Table 2. Mixed model analyses: associations between CP or cPVL and postural control

	Variables in model	CP Fixed effects (β)	CP OR (95%-CI)	Age Dif (mo)	cPVL Fixed effects (β)	cPVL OR (95%-CI)	Age Dif (mo)
First level postural control							
Direction-specificity trunk	Intercept	0.21	1.23 (0.76–2.01)		0.44	1.55 (0.97–2.51)	≤ 0.3[a] and ≥ 21.0
	Age	0.03**	**1.03 (1.01–1.06)**		0.01	1.01 (0.99–1.04)	
	CP / cPVL	-0.06	0.94 (0.59–1.48)		-1.19*	**0.30 (0.09–0.97)**	
	CP/cPVL × Age				0.09**	**1.09 (1.02–1.17)**	
Direction-specificity neck	Intercept	0.47	1.60 (0.98–2.68)	≤ 11.4 and	-0.13	0.88 (0.59–1.30)	
	Age	-0.08***	**0.92 (0.89–0.95)**	≥ 21.8	-0.05***	**0.95 (0.93–0.98)**	
	CP / cPVL	-1.27**	**0.28 (0.12–0.64)**		0.22	1.25 (0.84–1.86)	
	CP/cPVL × Age	0.08**	**1.08 (1.03–1.14)**				
Direction-specificity trunk + neck	Intercept	-0.77**	0.46 (0.28–0.77)		-0.44	0.65 (0.40–1.04)	≥ 13.0
	Age	-0.00	1.00 (0.97–1.03)		-0.02	0.98 (0.95–1.00)	
	CP / cPVL	0.30	1.36 (0.84–2.21)		-0.57	0.56 (0.17–1.81)	
	CP/cPVL × Age				0.09**	**1.09 (1.03–1.17)**	
Second level postural control							
Complete pattern	Intercept	0.26	1.30 (0.70–2.42)		0.13	1.14 (0.66–1.96)	
	Age	-0.03*	**0.97 (0.94–1.00)**		-0.03	0.97 (0.94–1.01)	
	CP / cPVL	-0.39	0.68 (0.39–1.15)		-0.85**	**0.43 (0.23–0.77)**	
Top-down recruitment	Intercept	-1.19***	0.30 (0.17–0.53)		-1.05***	0.35 (0.20–0.59)	
	Age	0.00	1.00 (0.97–1.04)		0.00	1.00 (0.97–1.03)	
	CP / cPVL	0.18	1.20 (0.86–1.69)		-0.07	0.94 (0.61–1.40)	
Bottom-up recruitment	Intercept	-0.97***	0.38 (0.22–0.65)		-1.14***	0.32 (0.19–0.53)	
	Age	0.02	1.02 (0.98–1.05)		0.02	1.02 (0.99–1.05)	
	CP / cPVL	-0.32	0.73 (0.50–1.01)		-0.21	0.81 (0.53–1.23)	
Simultaneous recruitment	Intercept	-2.86***	0.06 (0.02–0.16)		-2.85***	0.06 (0.02–0.16)	
	Age	-0.00	1.00 (0.94–1.07)		-0.01	0.99 (0.93–1.06)	
	CP / cPVL	-0.03	0.97 (0.51–1.86)		0.15	1.17 (0.51–2.45)	

Anticipatory activation trunk	Intercept	-1.11***	0.33 (0.18–0.59)	-1.20***	0.30 (0.18–0.51)
	Age	0.01	1.01 (0.98–1.05)	0.02	1.02 (0.99–1.05)
	CP / cPVL	-0.31	0.74 (0.47–1.14)	-0.65*	**0.52 (0.30–0.87)**
Anticipatory activation neck	Intercept	-1.12***	0.33 (0.18–0.59)	-1.11***	0.33 (0.18–0.58)
	Age	-0.02	0.98 (0.95–1.02)	-0.01	0.99 (0.95–1.03)
	CP / cPVL	0.09	1.09 (0.76–1.57)	-0.43	0.65 (0.38–1.06)
			CP Exp (β) (95%-CI)		**cPVL Exp (β) (95%-CI)**
Latency NF	Intercept	-1.09***	0.34 (0.24–0.47)	-1.09***	0.33 (0.24–0.47)
	Age	0.00	1.00 (0.98–1.02)	0.00	1.00 (0.98–1.02)
	CP / cPVL	0.16	1.17 (0.93–1.47)	0.30*	**1.35 (1.04–1.75)**
Latency NE	Intercept	-0.95***	0.39 (0.27–0.55)	-1.01***	0.36 (0.26–0.51)
	Age	-0.00	1.00 (0.97–1.02)	-0.00	1.00 (0.98–1.02)
	CP / cPVL	0.05	1.05 (0.83–1.33)	0.16	1.18 (0.89–1.56)
Latency RA	Intercept	-0.34**	0.71 (0.58–0.86)	-0.37**	0.69 (0.58–0.83)
	Age	-0.01*	**0.99 (0.98–1.00)**	-0.01	0.99 (0.98–1.00)
	CP / cPVL	0.09	1.10 (0.94–1.27)	0.10	1.11 (0.92–1.34)
Latency TE	Intercept	-1.31***	0.27 (0.20–0.36)	-1.25***	0.29 (0.22–0.37)
	Age	0.01	1.01 (0.99–1.02)	0.01	1.01 (0.99–1.02)
	CP / cPVL	0.18	1.20 (0.97–1.49)	0.27*	**1.31 (1.03–1.68)**
Latency LE	Intercept	-1.08***	0.34 (0.25–0.46)	-1.01***	**0.36 (0.28–0.48)**
	Age	-0.01	0.99 (0.98–1.01)	-0.01	0.99 (0.98–1.01)
	CP / cPVL	0.13	1.13 (0.93–1.38)	0.15	1.16 (0.92–1.46)

Significant effects of age or group in bold. *<0.05, **<0.01, ***<0.001

[a] 0.3 months is outside the range of our measurements and therefore not taken into account.

Latencies were modelled using the natural logarithm of (0.15 + median latency). Exp (β) has a similar interpretation as the OR: it represents the growth factor of the developmental trajectory, for age it reflects the growth factor per month.

Age Dif: The age in months at which the estimated average starts to significantly differ between CP and no CP group or cPVL and non-cPVL group (p<0.05). CP: cerebral palsy, cPVL: cystic periventricular leukomalacia, NF: neck flexor, NE: neck extensor, RA: rectus abdominis, TE: thoracal extensor, LE: lumbar extensor.

Recruitment patterns and orders, anticipatory activation

With increasing age, infants used less often the complete pattern, when corrected for CP (OR 0.97, CI: 0.94–1.00), but the prevalence of the complete pattern did not change during infancy when corrected for cPVL (OR 0.97, CI: 0.94–1.01). However, infants with cPVL used less often the complete pattern than infants without cPVL (OR 0.43, CI: 0.23–0.77), while infants with and without CP used similar rates (OR 0.68, CI: 0.39–1.15). Median values at 21 months CA in children with and without CP and with and without cPVL were 35%, 46%, 28% and 43%, respectively.

Recruitment order did not change with increasing age: all subgroups showed at all ages substantial variation in recruitment order. In other words, the top-down (median prevalence 24% at 21 months), bottom-up (median prevalence 27% at 21 months CA) and simultaneous (median prevalence 0% at 21 months CA) recruitment orders occurred equally often in early infancy as in late infancy, in infants with and without CP and in those with and without cPVL (Table 2). If infants did not use a top-down, bottom-up or simultaneous recruitment order, the order of muscle activation was mixed (i.e., the infant first activated the thoracal extensor).

Anticipatory activation at the trunk level did not change with increasing age (corrected for CP OR 1.01, CI: 0.98–1.05; corrected for cPVL OR 1.02, CI: 0.99–1.05), but infants with cPVL activated the trunk muscles less often prior to the onset of the reaching movement than infants without cPVL (OR 0.52, CI: 0.30–0.87). A similar difference was not significant for infants with and without CP (OR 0.74, CI: 0.47–1.14). The prevalence of anticipatory activation at the trunk level was usually 20–25%, but below 20% in cPVL and above 25% in non-cPVL at 21 months CA. At the neck level, the rate of anticipatory activation was similar across ages and groups (Table 2), with a median prevalence of 20% at 21 months CA.

Latencies of the postural muscles

With increasing age, only the latency of the RA decreased when correcting for CP (factor 0.99, CI: 0.98–1.00), it did not change when correcting for cPVL (factor 0.99, CI: 0.98–1.00). At 21 months CA median latency was 391 ms. The latencies of the other muscles remained similar throughout infancy. Infants with cPVL showed longer latencies to NF and TE recruitment than infants without cPVL (NF factor: 1.35, CI: 1.04–1.75; TE factor: 1.31, CI: 1.03–1.68). At 21 months median latency of NF was 414 ms in cPVL, 194 ms in non-cPVL; latency to TE was 241 ms in cPVL and 151 ms in non-cPVL. The presence of CP did not affect the recruitment latencies (Table 2).

Modulation of EMG-amplitude

At 21 months CA kinematic and amplitude data were available in 25 VHR-infants. An overview of which children showed significant correlations between EMG-amplitudes and kinematic parameters is presented in Table 3. Significant correlations were infrequent, and were in the expected and unexpected direction. The overview indicates that the majority of the VHR-infants did not show the capacity to modulate the EMG-amplitude to the degree of head sway, the number of MUs and the maximum or average velocity. Fisher's exact tests revealed that the prevalence of 'modulators' was not different for infants with and without CP or infants with and without cPVL (data not shown).

Discussion

The present explorative study indicates that the development of postural adjustments during reaching in VHR-infants who later were diagnosed with CP was virtually similar to that of VHR-infants without CP. However, postural development of VHR-infants with cPVL differed from that of VHR-infants without cPVL: with increasing age they started to use higher rates of direction-specificity at the trunk level and performed differently at the second level of postural control.

Cerebral palsy

Contrary to our hypothesis, VHR-infants with CP and without CP showed a virtually similar postural development during seated reaching. Rates of direction-specificity at 21 months in our VHR-infants (Figure 2) are comparable to the rates at 18 months of the high-risk infants (HR-infants) reported by van Balen et al.[7] In both studies, these values are lower than those of TD-infants,[4,7] supporting the idea that HR-infants are delayed in the development of the basic level of postural control.[6,7,10] Since VHR-infants with and without CP demonstrated a virtually similar development, and the majority of our infants without CP showed complex MND at 21 months, this suggests that all VHR-infants, including infants with complex MND, have an impaired postural control throughout infancy. Van Balen et al. noticed however that at early age, VHR-infants performed similar to TD-infants.[7] The combined results imply that it is not the group of infants with CP that grow into a deficit, but all VHR-infants (with CP, complex MND or a normal neurological outcome) – in line with van Balen et al.[7] The data may imply that the underlying mechanisms of postural problems in complex MND resemble those of CP.

Table 3. Correlation between EMG-amplitude of direction-specific postural muscles and kinematic parameters

Infant	CP	cPVL	Head sway			MU wrist			Maximum speed			Average speed		
			NE	TE	LE	NE	TE	LE	NE	TE	LE	NE	TE	LE
1	Yes	Yes	↑	-	↑	-	-	-	-	-	-	-	-	-
2	Yes	Yes	-	-	-	-	-	-	-	-	-	-	-	-
3	Yes	Yes				-	-	-	↓	-	-	-	-	-
4	Yes	Yes	-	↑	-	-	-	-	-	-	-	-	-	↓
5	Yes	Yes	-	-	-	-	-	-	-	-	-	↑	-	-
6	Yes	Yes				-	-	-	-	-	-	-	-	-
7	Yes	No	-	↓	↓↓	-	-	-	-	-	-	-	-	-
8	Yes	No	↑↑	-	↓↓	↑↑	↓↓	-	-	-	-	↓	-	-
9	Yes	No		-	-		-	-		-	-		-	-
10	Yes	No	-				-	-	-	-	-	-	-	-
11	Yes	No	-	-	-	↑↑	-	-	-	-	-	-	-	-
12	Yes	No	↑↑	-	↓	-	-	-	↑	-	-	↑	-	-
13	Yes	No	-	-	-	-	-	-	-	-	-	-	-	-
14	Yes	No	-	↑		-	-	-	-	-	-	-	-	-
15	No	No		-	-		-	-		-	-		-	-
16	No	No	-	-	-	↑	-	-	-	-	-	-	-	↓↓
17	No	No	-	-	-	-	-	-	-	-	-	-	-	-
18	No	No	↑	-	↑	-	-	-	-	-	-	-	-	-
19	No	No	-	-	-	-	-	-	-	↑	-	-	↑↑	-
20	No	No				-	-	-	-	-	-	-	-	-
21	No	No					-	-		-	-		-	-
22	No	No	-	-	-	-	↑	-	-	-	-	-	-	-
23	No	No	-	-	-	-	-	-	-	↓	-	-	-	-
24	No	No	-	-	-	↑	-	-	↓	↑	↑	-	-	↑
25	No	No	↑	-	-	-	↓	-	-	-	-	-	-	-

↑, ↑↑: positive correlation between amplitude (interval 1, 2 or 3 or a combination) and kinematic parameter: Spearman's rho $p<0.05$ and $p<0.01$ respectively. ↓, ↓↓: negative correlation between amplitude (interval 1, 2 or 3 or a combination) and kinematic parameter: Spearman's rho $p<0.05$ and $p<0.01$ respectively. –: no correlation between amplitude and kinematic parameter. A blank cell indicates that either the amplitude or kinematic parameter was missing.
CP: Cerebral Palsy, cPVL: cystic periventricular leukomalacia, NE: neck extensor, TE: thoracal extensor, LE: lumbar extensor, MU: movement unit.

An exception to the similar development of infants with and without CP was direction-specificity at neck level. Infants with CP had stable rates throughout infancy, while rates in infants without CP decreased with increasing age. Direction-specificity at neck level is more difficult to interpret than that at trunk level: the trunk is only involved in postural stabilization, but – in infancy – the neck may also assist in reaching activity by moving the head forward. However, it is conceivable that higher rates of direction-specificity in the neck in CP are a strategy to stabilize the head in space while reaching for a toy,[30] as it is well-known that children with CP experience difficulties with head stability.[31,32]

The two infants with GMFCS level V in the present study who did not develop the ability to sit independently showed direction-specific activity, which contradicts earlier findings.[9,10] A major difference between the current two children and the two cases previously described, was the presence of dystonia in the latter infants (M. Hadders-Algra, personal communication), whereas a dystonic component was absent in the former. Another major difference between the infants is the brain lesions: one of the infants from the literature was a near-term infant with a normal cranial ultrasound scan,[10] whereas the second was a preterm infant with predominantly germinal matrix and intraventricular haemorrhage with ventricular dilatation, with secondary periventricular cyst formation.[9] Both infants in the current study were classified as having cPVL. On the basis of the previous case-reports it was suggested that direction-specificity is a prerequisite for the development of independent sitting. It might be true that a total absence of direction-specificity precludes the development of independent sitting. However, the current two cases indicate that the presence of direction-specificity is not a guarantee for the development of independent sitting, as it seems unlikely that the two children of the current study will develop this ability. Our limited findings support the conclusion of a previous study that showed that the rate of direction-specific activity was not associated with the development of independent sitting.[26] This supports the idea that other factors, e.g., learning to cope with inertial forces of the body, play a prominent role in the development of the ability to sit independently.[33] The limited data on infants functioning at GMFCS level V underline the need of more research on postural development of these children in order to better understand their performance profiles, which in turn will provide clues for the most appropriate type of support.

Also at the second level VHR-infants with CP and without CP showed a similar development. It differed from that of TD-infants, who for instance gradually develop a preference for bottom-up recruitment at 18 months,[4] whereas the VHR-infants lacked such development. TD-infants also develop the capacity to modulate EMG-amplitude from 9 months onwards on a moving platform or at 18 months

during reaching,[34, 35] while the VHR-infants of the current study had not developed this capacity at the age of 21 months. Since pre-school and school aged children with CP are able to modulate postural muscle contraction to some extent, this can be interpreted as a delay in development.[6] The findings of our study are in line with van Balen et al. indicating that HR-infants performed worse than TD-infants at the second level of postural control.[7] The data suggest that all VHR-infants, including infants with complex MND, have postural problems. The developmental delay at the second level may be interpreted as a combination of dysfunction and adaptation. The lacking ability to modulate EMG-amplitude presumably is a dysfunction. The presence of this dysfunction forces VHR-infants to search for other strategies to cope with postural challenges. The latter may for instance be reflected by the primary focus to stabilize the head in space by increasing direction-specificity at neck level.

Cystic periventricular leukomalacia

Our subgroup of VHR-infants with the most severe brain lesion cPVL – who all developed CP – showed an increase in direction-specificity at trunk level with increasing age, while other VHR-infants had stable rates throughout infancy. Infants with cPVL had higher values from 21 (trunk level) or 13 months onwards (trunk and neck level). Rates of infants with cPVL at 21 months approached the rates of TD-infants at 18 months (trunk 80% vs. 88%, trunk and neck 64% and 58% respectively).[4] Previous research suggested that direction-specificity has an innate origin, TD-infants of 1 month already exhibit direction-specific activity.[36] Our data indicate that the basic and innate level is preserved in infants with cPVL. However, they showed substantial dysfunctions at the second level: they used less often the complete pattern, anticipatory activity at trunk level and had longer latencies to recruit the neck flexor and thoracal extensor muscles than other VHR-infants. Conceivably, the impairments at the second level resulting from the white matter injury shift the focus of postural control to the first level. Studies in young TD-infants in whom the second level is only minimally available, showed that these infants may use the rate of direction-specificity to cope with postural challenges: the rate of direction-specificity is much higher during external perturbations on a balance platform than during seated reaching.[4,37]

Our data indicated that infants with cPVL do not grow into a postural deficit with increasing age, the second level of postural control is impaired from early age onwards. Cystic PVL results in extensive injury of neural circuitries, presumably

explaining why functions that rely on complex circuitries, such as postural adjustments, postural behaviour during the pull-to-sit manoeuvre[20] and the pupillary light response[21] are impaired from early age onwards.

Methodological considerations

A strength of this study is the longitudinal data collection which allowed us to study developmental trajectories of postural control in VHR-infants. Another strength is the use of generalized linear mixed model analyses that provided the opportunity to take repeated measurements at different ages and missing values into account. The small sample size and the heterogeneity in CP limit conclusions on high-risk infants and the general population with CP, also considering the overrepresentation of infants with cPVL due to our strict inclusion criteria. The small sample size also limits exploration of the effect of GMFCS-levels within infants with cPVL and other VHR-infants. Another limitation is that the data are derived from an RCT studying the effects of two early intervention programs. However, outcome of infants in both intervention groups was similar.

Concluding remarks

This study indicated that the development of postural control is virtually similar in VHR-infants with and without CP. In comparison to TD-infants, both groups of VHR-infants gradually grow into a postural deficit which may reflect increasing dysfunction and/or a delay in development. However, infants with cPVL showed substantial dysfunctions at the second level of postural control throughout infancy. Presumably as a consequence, they primarily relied on the first level by using increased rates of direction-specificity. In terms of early intervention, our results may be interpreted in the following way. Possibly, HR-infants without cPVL may benefit from early postural training, since their major postural problem is a delayed development. Postural training may be performed for instance by challenging the infant's head balance in the first months post term, e.g., by provision of little head support during daily activities as carrying and bathing. Postural control may also be trained by bathing young infants in sitting position,[38] and by challenging the older infant to search for the limits of stability in different positions and situations. If postural training is incorporated into daily life situations in a playful way, the infant will presumably benefit most. However, infants with cPVL who have substantial impairments at the second level of postural control throughout infancy, may profit

most from using adaptive seating systems providing external or specific postural support during reaching tasks or other tasks that require a stable sitting position. The provision of adequate postural support compensates the postural deficit and promotes the child's ability to perform goal directed actions, such as needed for eating and playing.[39] In addition, sitting skills may also be trained in functional and play activities.

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